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Rheumatic Heart Disease

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Rheumatic heart disease (RHD) is the most common form of heart disease among children and young adults in many developing countries. It affects more than 4 million people worldwide and causes approximately 90,000 deaths each year. This heavy toll could be reduced, because RHD is always triggered by a controllable infectious agent: group A streptococci.

The chain of events leading to RHD is complex and evolves over several years. It starts with acute group A streptococcal pharyngitis (GASP), or strep throat, which is extremely common among school-age children. If they are not treated effectively, 3 percent of GASP episodes lead to rheumatic fever (RF), a disease that damages the heart, particularly the heart valves. Heart valve injuries occur because group A streptococci precipitate an immunological assault against the body's own heart valves and some other tissues.

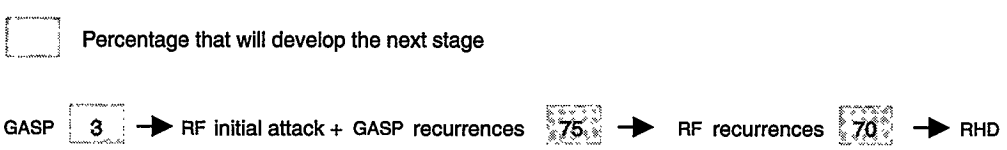
Rheumatic fever lasts for only several weeks but often leaves permanent scars which cause rheumatic heart disease. Damaged valves no longer open or close properly, thus disrupting normal blood flow. These hemodynamic changes overload the heart and lead to progressive cardiac insufficiency and often to premature death. Finally, the severity of valve injuries tends to increase over time, because RF recurs in 75 percent of children who had a first attack of RF when they suffer new episodes of streptococcal pharyngitis (figure 10-1). In the absence of any intervention, among 1,000 children with pharyngitis, 200 would have pharyngitis caused by group A streptococci, 6 would suffer an initial RF attack, 5 would later have recurrences of RF, and 2 would die from intractable cardiac failure.

Interventions to prevent RHD can be directed at different points in the chain of events leading from GASP to intractable cardiac failure. Primary prevention targets cases of pharyngitis and consists of a single injection of benzathine penicillin, which effectively treats GASP and prevents the occurrence of RF. Secondary prevention targets RF cases and consists in monthly injections of benzathine penicillin for several years to prevent recurrences of GASP that might trigger new bouts of RF. Tertiary prophylaxis targets severe cases of RHD. It interrupts the progression to intractable cardiac failure by means of surgical repair or replacement of damaged heart valves. A vaccine that could prevent the occurrence of GASP is not yet available.

The cost-effectiveness of various strategies is determined by the number of total cases that have to be treated to prevent one death and is limited by difficulties in finding the cases. Primary prevention in developing countries is impractical when the diagnosis of GASP cannot be confirmed. Secondary prevention therefore remains the cornerstone of RHD prevention. Tertiary prophylaxis is a cost-effective alternative in spite of the high cost of surgery because it can be very specifically directed to a small number of cases.

In industrial countries the incidence of RF and prevalence of RHD decreased during the past decades as socioeconomic conditions improved and penicillin treatment became available. Fewer than 1,000 cases of RHD, and almost no deaths, now occur each year in industrial countries. The challenge is to achieve a similar reduction in developing countries, despite

Figure 10-1. Chain of Events Leading to Rheumatic Heart Disease Showing Percentage That Will Develop the Next Stage



Source: Authors, from epidemiologic data.

scarce resources, slow socioeconomic growth, and limited access to health care.

In this chapter we review the epidemiology, pathogenesis, and clinical manifestations of RF and RHD; discuss possible interventions and analyze their cost-effectiveness; and, finally, outline areas which require further research.

Background

The distribution of RF and RHD is quite different in industrial and developing countries, and has evolved over time. The distribution of the disease also varies within each country between rural and urban areas and among different population groups. The major determinants of the disease are socioeconomic conditions, access to medical care, and the changing virulence of group A streptococci.

In Industrial Countries

Rheumatic fever and rheumatic heart disease have virtually disappeared in industrial countries. The average annual RF incidence is now below 0.5 per 100,000, and RHD prevalence is less than 0.05 per 1000.

The progressive decline in RF and RHD started simultaneously in several Western countries at the beginning of the twentieth century, several decades before penicillin treatment became available. With the introduction of penicillin, at the end of World War II, the decline accelerated rapidly among higher socioeconomic groups but lagged behind among the poor. Inadequate housing and overcrowding favor the spread of streptococcal infection from person to person, undernutrition impairs the immune response, and streptococci remain longer in the throat in the absence of penicillin treatment. The number of rheumatic fever and rheumatic heart disease cases have nevertheless slowly decreased even in communities in which the use of penicillin was not widespread, perhaps as a consequence of lower virulence of group A streptococci. These observations indicate that penicillin treatment was only one among several factors that prompted the decline of RF and RHD (Gordis 1985; Gordis, Lilienfeld, and Rodriguez 1969a and 1969b; Massell and others 1988).

The frequency of occurrence of pharyngitis has also decreased in industrial countries, but not the proportion of pharyngitis caused by group A streptococci. Streptococci cause 15 to 30 percent of all pharyngitis, and this proportion does not vary significantly within and between nations worldwide (Markowitz 1985). The potential to develop RF and RHD therefore persists in industrial countries, as was evidenced by outbreaks of RF that have occurred in several small communities since 1986 in the United States and northern Italy. In each instance, RF followed a similar new epidemiologic pattern: RF cases were concentrated among middle-class families with ready access to medical care. The resurgence of RF, following this new pattern, has raised great concern and requires close monitoring (Hosier and others 1987; Kaplan and Markowitz 1988; Veasy and others 1987; Wald and others 1987).

In the Developing World

In sharp contrast to the situation prevailing in industrial countries, RF and RHD are quite common in developing countries, where the incidence of RF ranges from 6.9 to 100 cases per 100,000 people (table 10-1), and the prevalence of RHD ranges from 1.0 to 18.6 cases per 1,000 (table 10-2). These rates are similar to rates that were common in Western countries at the beginning of this century (WHO 1988). Their broad range illustrates disparities existing among different geographic regions, among various ethnic and socioeconomic groups, and between urban and rural populations. For instance, several minority groups in the Pacific Islands still suffer from a very high prevalence of RHD, ranging between 7.6 and 18.6 cases per 1,000 persons, even though the prevalence of RHD is quite low in the general population. In New Zealand, most cases of RHD were reported from the northern part of North Island, where Maori and Polynèsian populations are concentrated (Neutze 1988a). In Australia, RF and RHD persist only among aboriginal communities living in the Northern Territory (MacDonald and Walker 1989). The differences observed between various ethnic groups are probably attributable to their lower socioeconomic conditions, rather than to a particular genetic susceptibility to the disease.

The prevalence of RHD is determined worldwide by the level of socioeconomic development and by access to health care, but in addition, it differs strikingly between urban and rural settings. The prevalence of RHD tends to be higher among the urban poor than among rural poor. It ranges from 8.5 to 11 cases per 1,000 individuals in the largest cities of Africa, Asia, and Latin America, whereas in rural areas, RHD prevalence does not exceed 3.5 per 1,000 on average (Strasser 1985).

Table 10-1. Annual Incidence of Rheumatic Fever in Selected Areas

Location	*Year*	*Incidence (per 100,000)*	*Age group (years)*
England and Wales	1963	4.7	1–14
Baltimore (United States)	1964	15.3	5–19
Denmark	1970	10.7	All
Singapore	1971	92	All
Cyprus	1972	27–43	All
Hong Kong	1972	23	All
Czechoslovakia	1972	8.5	<15
Iran, Islamic Rep. of	1973	59–100	All
Kuwait	1983	19.6	<14
Auckland (New Zealand)[a]	1984	70.7	<15
Hawaii (United States)[b]	1976–80	14.4	4–18
Salt Lake County (United States)	1985	18.1	5–17

a. Maori population.

b. Incidence (per 100,000) by ethnic group was Samoan, 96.5; Hawaiian, 27.2; Filipino, 9.0; and Chinese, 6.9.

Source: Adapted from Majeed and others 1987.

Table 10-2. Prevalence of Rheumatic Heart Disease in School-age Children in Different Areas

Location	Year	Prevalence (per 1,000)
Africa		
Algeria	1970	15.0
Nigeria	1970	0.–3.0
Egypt	1973	10.0
Morocco	1973	9.9
Soweto, South Africa	1975	6.9
Côte d'Ivoire	1985	1.9
Latin America		
Brazil	1968–70s	1.6–6.8
Montevideo, Uruguay	1970	1.0
	1985	10.0
La Paz, Bolivia	1973	17.0
Mexico City, Mexico	1977	8.5
San Juan, Puerto Rico	1980	1.6
Caracas, Venezuela	1985	10.0
Porto Allegre, Brazil	1985	10.0
São Paulo, Brazil	1985	10.0
Asia		
Tokyo, Japan	1966	0.3
Taiwan, Republic of China	1970	1.4
India	1970s	6.0–11
Pakistan	1970s	1.8–11
Thailand	1974	1.2–2.1
China	1979	0.4–2.7
Mongolia	n.d.	3.5
New Delhi, India	1985	11.0
Pacific		
Torres Strait Islands, Australia	1978	4.7–12.5
Rarotonga, Cook Islands	1982	18.6
French Polynesia	1988	11.2
Waikito, New Zealand[a]	n.d.	7.6 (Maori) 1.0 (non-Maori)

n.d. No date available.
a. Subjects in this study were age five to twenty-nine years.
Source: Adapted from WHO, 1988.

Trends observed during the past several decades in developing countries vary. The prevalence of RHD is increasing in the largest cities undergoing rapid growth, particularly in slum areas. In India the prevalence of RHD has increased with rapid urbanization, and now reaches 6 cases per 1,000 people on average for the whole country (WHO 1980a). The prevalence of RHD seems to be much lower in China than it is in India. Richard Bumgarner estimated in 1990 that there were 410,000 cases of RHD in China, which corresponds to an average RHD prevalence of 1.4 per 1,000 for the whole country (Bumgarner, personal communication). In middle-income economies—for example, Thailand—the prevalence of RHD is decreasing.

Pathogenesis

Group A streptococci are very common human pathogens. Between 20 and 30 million cases of group A streptococcal infections occur each year in the United States alone. These cases include infections of the skin and throat (GASP), forms of pneumonia, and a recently identified disease resembling toxic shock. Scarlet fever is the result of infection by streptococci that elaborate an erythrogenic toxin against which the host has no antibodies.

The exact nature of the interaction between group A streptococci and the human host leading to RF is not fully understood. Several hypotheses were developed to explain how streptococci might damage the heart:

- Direct tissue invasion by group A streptococci
- Toxic effects of streptococcal products, particularly streptolysins S or O, which are known to be capable of inducing tissue injury
- Reactions like serum sickness, mediated by antigen-antibody complexes
- Autoimmune phenomena induced by similarity or identity between certain streptococcal antigens and human tissue components

Even though direct tissue invasion and toxic effects of streptolysins may play a role, most attention has recently been directed to the immunological process involved. Almost every part in the immune system, cellular and humoral, is involved in RF. Group A streptococci selectively amplify or downregulate various immune pathways which are likely to be critical in the subsequent development of RF after an episode of streptococcal pharyngitis (Cairns 1988; Goldstein 1967).

Recent research has unraveled the key role played by M proteins in the immunological process (Fischetti 1991). M proteins cover the surface of the bacterial cell wall and appear as hairlike projections. They give a streptococcus the ability to resist ingestion by white blood cells. To overcome the effect of M proteins, the human host produces antibodies directed against M proteins. These antibodies neutralize the protective capacity of the M protein and allow the streptococcus to be engulfed and destroyed by white blood cells. Group A streptococci have further increased their ability to evade the immune system through antigenic variation. There are more than eighty different serotypes, or varieties of M proteins, and laboratory tests suggest that antibodies against one serotype do not offer protection against others. The low incidence of GASP observed in adulthood may be due either to an undefined, age-related factor or to a broad immunity that individuals acquire through contact with streptococci as children.

Different serotypes of group A streptococci cause the two major nonsuppurative sequelae of GASP: RF and glomerulonephritis. Serotypes of group A streptococci isolated from children with RF and their families differ from those isolated from children with poststreptococcal nephritis and their families (Majeed and others 1987). This chapter deals only with RF.

Rheumatic fever occurs when antibodies developed against M proteins cross-react with the host's own heart tissues because some fragments (epitopes) of the M protein closely resemble fragments of valve glycoproteins and valve fibroblasts, leading

Table 10-3. Frequency of Major Manifestations in Initial Attacks of Rheumatic Fever in Prospective Studies
(percent)

Manifestation	Kuwait	India	United Kingdom	United States
Carditis	46	34	55	42
Polyarthritis	79	67	85	76
Chorea	8	20	13	8
Nodules	0.5	3	**	1
Erythema marginatum	0.5	2	**	4

** Negligible amount.
Source: Adapted from Markowitz 1988.

to permanent valvular damage. The exact role of such cross-reactive antibodies in the genesis of RHD, however, is not yet understood (Fischetti 1991).

Other researchers have identified genetic markers—B lymphocyte alloantigens—which might determine greater susceptibility to RF (Patarroyo and others 1979). For instance, RF happened more often in monozygotic than dizygotic twins, but the numbers studied were very small (Taranta and others 1959). These findings still require confirmation in various ethnic groups.

There is no single determinant for RF. Several risk factors pertaining to the environment, the host, and the agent interact and ultimately cause RF. Only a few of the mechanisms involved are fully understood. For instance, the observation that the sera of patients contained antibodies against heart tissues dates back half a century, but the exact amino-acid sequence of heart cross-reactive epitopes was identified in M proteins only recently.

Clinical Aspects

Rheumatic fever occurs in 3 percent of all GASP episodes (Denny 1987). No direct relationship exists between the severity of GASP symptoms—fever, sore throat—and the development of RF ten to thirty-five days later. Furthermore, GASP causes no symptoms in 30 to 50 percent of all children who later develop RF (Maharaj and others 1987).

The clinical findings vary greatly and are determined by the site of involvement, the severity of the attack, and the stage at which the patient is first examined. The most common symptoms of RF are redness and pain of the joints (arthritis) and a typical heart murmur (carditis). The clinical diagnosis of RF may be difficult because the severity and the combination of RF symptoms vary among different individuals. The onset is usually acute when arthritis is the presenting manifestation and more gradual when carditis is the initial clinical feature. When carditis is the sole clinical manifestation, it can be difficult to determine when the attack began.

Arthritis and carditis are sometimes accompanied by chorea, subcutaneous nodules, or erythema marginatum. Chorea occurs in 10 to 15 percent of patients and is self-limited. The rapid random, nonrhythmic movements of chorea most often affect the muscles of the face and arms. Subcutaneous nodules are round, hard, painless swellings, which occur in 5 to 10 percent of rheumatic patients. Erythema marginatum is the characteristic skin rash of RF and occurs in fewer than 5 percent of patients. Symptoms observed during the initial attack of RF tend to be different from those observed during subsequent episodes of RF (Nelson 1983).

Initial Rheumatic Fever Attack

During the initial attack of RF it is common to observe migrating arthritis with painful, red, hot swellings of one or several large joints—knees, elbows, wrists, and ankles. Arthritis may last up to three months; it causes significant morbidity but ultimately leaves no sequelae (WHO 1988). Arthritis tends to be less frequent in subsequent episodes of RF. The frequency of carditis, on the contrary, tends to increase with recurrent episodes of RF.

Carditis often causes few symptoms, and it is rarely life threatening. The onset of carditis may be asymptomatic—so-called silent carditis—or insidious, with only a few vague symptoms such as lethargy, poor appetite, and chronic respiratory infections. In this instance, patients seek health care only much later, when they suffer from shortness of breath (Markowitz 1988).

Recurrent RF Episodes

After the initial attack, RF is characterized by frequent recurrences of the disease after a varying number of intercurrent years of freedom from symptoms. The risk for RF recurrence, following subsequent GASP, increases dramatically from 3 percent to 75 percent (Denny 1987). Recurrent bouts of carditis often cause long-term sequelae because when the inflammatory process heals in the heart, it leaves scars on the valves, which impair their normal opening or closure.

Table 10-4. Outcomes of 10,000 Hypothetical Cases of Rheumatic Fever without Treatment

	Initial attack without recurrence		Initial attack with recurrence		Total	
Outcome	Number	Percent	Number	Percent	Number	Percent
Total cases	2,500	25	7,500	75	10,000	100
Recover	1,475	59	1,500	20	2,975	30
Carditis	1,025	41	6,000	80	7,025	70
Mild	369	15	840	11	1,209	12
Moderate/ severe cardiomegaly	431	17	1,920	26	2,351	24
Congestive heart failure leading to death	22	9	3,240	43	3,465	35

Source: Authors, from epidemiologic data.

Table 10-5. Age Distribution at First Attack of Rheumatic Fever and Death in 10,000 Hypothetical Cases without Treatment

Ages (years)	Number	Percent
At first attack		
< 5	800	8
6–8	2,000	20
9–11	3,600	36
12–15	2,600	26
> 15	1,000	10
Total	10,000	100
At death		
< 5	87	2.5
5–14	485	14
15–44	1,975	57
45–64	814	23.5
>65	104	3
Total	3,465	100

Source: Authors, from epidemiologic data.

In developing countries, the initial episode of RF is often unnoticed, and arthritis tends to be reported less often than in Western countries. Because of these differences, RF seemed to follow a different clinical course in developing countries. Careful longitudinal studies have not substantiated such differences. Carditis occurs in 34 to 55 percent of children during the initial RF attack and in 65 to 85 percent of subsequent RF episodes in different parts of the world (Majeed and others 1981; Padmavati and Gupta 1988; Potter and others 1978; Sanyal and others 1974; see table 10-3). Carditis, nevertheless, runs a more severe course in developing countries because the initial attack of RF occurs at a much younger age, and RF recurs more often.

Rheumatic Heart Disease

Approximately 90 percent of children who have carditis during RF episodes will develop RHD. This disease is a chronic and progressive condition resulting from permanent scarring of heart valves, following RF. It often causes little morbidity in its early stages. Children attend school, run, and play (McLaren and others 1978). A few, however, suffer from exhaustion when they exercise. As RHD becomes more severe with recurrent bouts of RF, children and young adults can no longer attend school or work, and they withdraw from play and other social activities. Finally, severe congestive cardiac failure occurs, and medical treatment often fails. Heart surgery then remains the only possible intervention.

Disease Outcome

The age at which the first RF attack occurs and the frequency and severity of RF recurrences determine the outcome of RHD. Young children six to thirteen years old are at highest risk for recurrences, and they suffer a more fulminant course of the disease. Table 10-4 illustrates the outcome of 10,000 RF hypothetical episodes based on different epidemiologic studies. These studies have shown that initial episodes of RF occurred before age fifteen in 90 percent of cases (table 10-5). Thirty percent of all children having one or more RF episodes recover completely even in the absence of treatment; 12 percent develop mild carditis; 23 percent develop cardiomegaly but no congestive heart failure. Among the remaining 35 percent, the damage to the heart valve is so severe that it causes progressive heart failure and early death.

Diagnosis

The diagnosis of RF requires a combination of clinical and laboratory criteria because no single symptom or laboratory test is pathognomonic of the disease. Rheumatic carditis, or permanent valvular lesions of RHD are suspected when a heart murmur is audible at auscultation. The initial detection of heart murmurs can be successfully done by health workers (Irwig and others 1985). To confirm the diagnosis and to determine the extent of underlying heart damage, however, chest x-ray, electrocardiogram, and, if possible, echocardiography or cardiac catheterization are required.

Jones Criteria

Dr. T. Duckett Jones systematized clinical diagnosis of RF in 1944 and classified the observed symptoms into major and minor manifestations. Jones criteria have been only slightly modified by subsequent revisions and remain the mainstay for the diagnosis of rheumatic fever today (tables 10-6 and 10-7; figure 10-2). Standardized diagnostic criteria are important to ensure comparability of epidemiological data, for the evaluation of prevention and care programs, and to guide therapeutic decisions. Underdiagnosis will prevent affected children from

Table 10-6. Changes in the Original Jones Criteria for the Diagnosis of Acute Rheumatic Fever

	Year			
Manifestation	1944	1951	1956	1965/1984
Carditis	M	M	M	M
Polyarthritis	—	M	M	M
Chorea	M	M	M	M
Subcutaneous nodules	M	M	M	M
Erythema marginatum	m	—	m	m
Arthralgia	M	—	m	m
Fever	m	m	m	m
Erythrocyte sedimentation rate	m	m	m	m
History of acute rheumatic fever or rheumatic heart disease	M	m	m	m
Evidence of prior streptococcal infection	—	m	m	R

— Not available.

Note: M = Major manifestation; m = minor manifestation; R = required manifestation.

Source: WHO 1988.

Table 10-7. Cases of Rheumatic Heart Disease in the Developing World, 1985

Location	Population age 6–16 years (thousands)	Total cases[a] (thousands)	Deaths[b] per year (thousands)
Asia			
Urban	189,000	1,510	—
Rural	485,000	971	—
Total	674,000	2,481	56
Latin America			
Urban	73,000	584	—
Rural	33,000	66	—
Total	106,000	650	15
Middle East/ North Africa			
Urban	32,000	253	—
Rural	81,000	162	—
Total	113,000	415	9
Sub-Saharan Africa			
Urban	40,000	319	—
Rural	100,000	200	—
Total	140,000	519	12
Total		4,065	92

— Not available.

a. These are conservative estimates, based on the following assumptions: (a) mean urban prevalence 8/1,000; (b) mean rural prevalence 2/1,000. Those severely affected will die within twenty years of the initial attack of RF.

b. Assumes 45 percent of cases each year result in death within 20 years. Calculation for number of deaths per year is as follows: Total number of cases in the region/20¤0¤45.

Source: Authors, from epidemologic data.

receiving proper treatment, whereas overdiagnosis may create unnecessary emotional and psychological suffering among patients and parents (Jones 1944).

GASP: Laboratory Diagnosis

Laboratory tests can provide direct identification of group A streptococci or retrospective evidence of infection with group A streptococci. Direct identification of group A streptococci from the throats of children suffering from pharyngitis is required to diagnose GASP. This can be done through cultures, or by means of rapid antigen detection tests. Cultures on blood agar plates are exceptionally effective as a diagnostic tool. However, they require laboratory facilities, and bacteriologic identification takes eighteen to twenty-four hours. Rapid antigen detection tests provide an immediate diagnosis. They have a good specificity of 98 percent, but their sensitivity varies with the amount of antigen present between 44 percent and 100 percent. Negative results, therefore, must be confirmed by a culture (Kaplan and Markowitz 1988). The sensitivity of rapid antigen detection tests needs to be increased to ensure reliable diagnosis and improved clinical management.

Retrospective evidence is important to confirm the diagnosis of RF. Titers of antistreptolysin O (ASO), which is an antibody developed against extracellular products of group A streptococci, peak within three weeks following GASP and provide retrospective evidence of infection with group A streptococci. A single ASO titer does not provide a reliable measure of the time elapsed since infection because the rate of decrease of ASO titers is highly variable (Denny 1987).

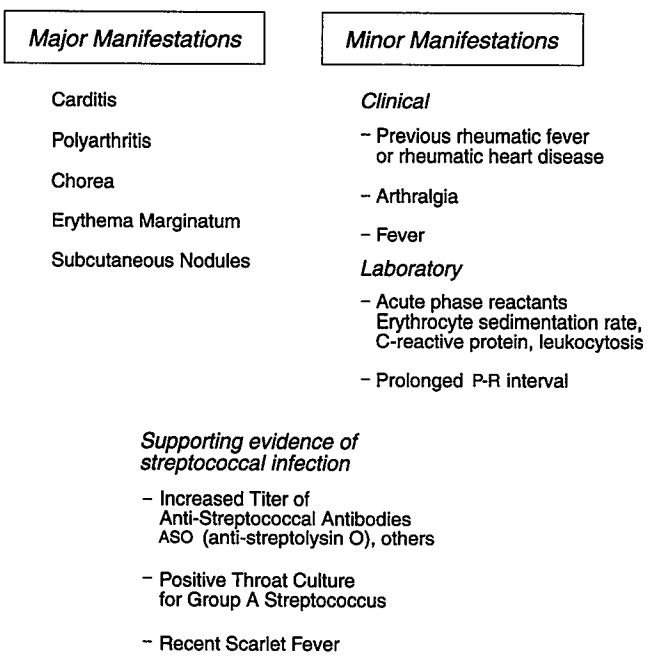
The Public Health Significance

Children bear the major burden of disease resulting from RF and RHD. This burden is likely to increase with continuing population growth in developing countries. RF and RHD have high economic costs which could be reduced through effective prophylaxis of RF and RHD.

Current levels in the Developing Countries

The first African case of RHD was reported by Procter and Hargreaves in eastern Africa in 1932, but the importance of RF and RHD in developing countries was not recognized until the 1950s (Anabwani, Amoa, and Muita 1989). Rheumatic heart disease is the most common form of heart disease among children and one of the most common cardiovascular diseases

Figure 10-2. Jones Criteria (Revised) for Guidance in the Diagnosis of Rheumatic Fever



Note: Two major or one major and two minor manifestations plus evidence of preceding streptococcal infection indicates a high probability of acute rheumatic fever.

This figure shows the recommendation of the American Heart Association (Circulation 1984). It has been approved by the WHO Study Group (1988) with the provision that the following be dealt with separately and be exempted from fulfilling the Jones criteria: "pure"chorea, late on-set carditis, and rheumatic recurrence.

Source: WHO 1988.

Table 10-8. Hospital Admissions for Rheumatic Heart Disease
(percent)

Country	Admissions as percentage of all cardiac admissions
Asia	
Bangladesh	34.0
Burma	30.0
Mongolia	30.0
Pakistan	23.0
Thailand	34.0
Africa	
Ethiopia	34.8
Ghana	20.6
Malawi	23.0
Nigeria (Ibadan)	18.1
Nigeria (Kano)	23.0
South Africa	25.0
Tanzania	9.7
Uganda	24.7
Zambia	18.2

Source: WHO 1980a; Hutt 1991.

among young adults in tropical and subtropical countries (Sharper 1972). In 1985 an estimated 4.2 million people—mostly children and young adults—were suffering from RHD; 500,000 of these people had at least one episode of RF, and approximately 90,000 of those affected died (table 10-8).

The outstanding features of RF and RHD in tropical and subtropical regions are the young age at which the initial attack of RF occurs, the high recurrence rate, and the more fulminant course of RHD. In Thailand, peak RF incidence occurred between ages nine and eleven, and peak RHD prevalence between twelve and sixteen (Vongprateep, Dharmasakti, and Sindhavanonda 1988). A similar age distribution was observed in other developing countries.

Rheumatic fever and rheumatic heart disease cause severe disability and are a frequent cause for hospitalization. About 10 to 35 percent of all clinical cardiac patients in hospitals in Sub-Saharan Africa and Asia were suffering from RHD (Hutt 1991; see table 10-9). In Barangwanath Hospital, Soweto, in the Republic of South Africa, RF and RHD accounted for 11 per 1,000 of all pediatric patients under age ten (Edington and Gear 1982). The average length of hospital stay of three to four weeks, for both RF and RHD, meant prolonged absence from school or work.

In the 1960s, cardiac valvular surgery became available. The high number of children and young adults referred for surgery confirmed the young age of occurrence and the severity of RHD in developing countries. In Nairobi, Kenya, 33 percent of all valvotomies were done in children under age sixteen; in Johannesburg, South Africa, 44 percent of patients that underwent valvuloplasty were fifteen or younger, and 26 percent were under twelve (Anabwani, Amoa, and Muita 1989; Antunes and others 1987). Heart surgery was not available, however, in many developing countries, and children were sometimes referred abroad at high cost. For instance, by mid-1985, 238 RHD cases from French Polynesia had been evacuated to France to undergo heart surgery (Vigneron 1989).

Women of childbearing age are at the highest risk of suffering complications from RHD during pregnancy. The important hemodynamic changes occurring during pregnancy may precipitate cardiac failure in women with RHD. Rheumatic heart disease is an important obstetric complication in Africa, making up 75 to 90 percent of all symptomatic heart disease cases during pregnancy. In Cape Town, South Africa, closed mitral valvotomies were performed in 41 women age eighteen to forty-one between 1965 and 1985 (Vasloo and Reichart 1987).

Approximately 90,000 deaths due to RHD occur each year among all those affected. Peak mortality reported from autopsy studies in Mulago Hospital, Kampala, Uganda, occurred between ages twenty-four and thirty-four (Shaper 1972; see figure 10-3). Adults living beyond age thirty-five tend to suffer from less severe cardiac damage and, therefore, have lower mortality rates. The death rate from RHD is highest among young adults. In Sub-Saharan Africa, up to 20 percent of all deaths confirmed at autopsy were due to RHD (Hutt 1991). Rheumatic heart disease causes approximately 1 out of 150 deaths occurring between the ages of sixteen and forty-nine in developing countries.

Table 10-9. Cost-Effectiveness of Different Prophylactic Strategies

Treatment	Unit cost (dollars)	Cases treated to prevent one death[a]	Cost per death averted (dollars)	DALYs gained[b]	Cost per DALY (dollars)
Prevention of pharyngitis[c]	60	682	40,920	39	1,049
Prevention of RFd	1,380	4	5,520	39	142
Prophylaxis of RHDe	8,500	1.5	12,750	30	425

a. Assuming 100 percent efficacy of each treatment, approximately 500 pharyngitis cases, 100 GASP, three RF, or one severe RHD case would have to be treated to prevent one death.

b. Twenty DALYs per death averted. DALYs per disability reduction: three for mild carditis (10 percent for thirty years); six for moderate carditis (20 percent for thirty years); ten for severe carditis (50 percent for twenty years). The first two prevention strategies provide a gain of thirty-nine DALYs because these interventions reduce the disability from mild and moderate carditis in addition to reducing disability and death from severe carditis; the last strategy does not reduce disability from mild or moderate carditis.

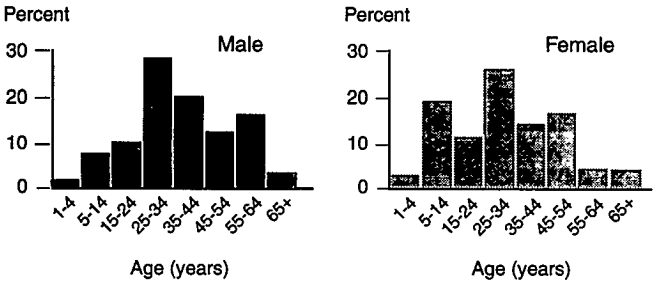
c. Primary prevention entails one benzathine-penicillin injection each year for ten years. Efficacy of intervention is 70 percent.

d. Secondary prevention entails one benzathine-penicillin injection per month for five years and assumes one hospitalization of twenty-four days. Efficacy of intervention is 80 percent.

e. Tertiary prophylaxis entails valvuloplasty or valve replacement and includes hospitalization. Efficacy of intervention is 70 percent. Unit costs range from $5,000 to $12,000; costs per death averted from $7,500 to $18,000; and costs per DALY from $250 to $600.

Source: Authors, from epidemiologic data.

Figure 10-3. Ages of Subjects with Rheumatic Heart Disease at Autopsy in Mulago Hospital, Kampala, Uganda, 1960–65



Source: Sharper 1972.

Possible Patterns of Morbidity and Mortality by 2015

Total morbidity and mortality attributable to RF and RHD is likely to increase during the next twenty-five years because the total population at highest risk for RF, those between the ages of five and fifteen, will increase and reach 1.2 billion by the year 2015. Half of them will live in urban areas (United Nations 1988). Assuming no changes in the incidence or in the prevention of RHD by the year 2015, approximately 6 million school-age children will suffer from RHD. The level of socioeconomic development, access to health care, and progress toward better preventive strategies (that is, a vaccine) will ultimately determine the disease burden resulting from RF and RHD.

Economic Costs

Rheumatic fever and rheumatic heart disease incur direct as well as indirect costs. Estimates of direct costs of RHD are not available in most developing countries. Neutze estimated the financial cost incurred to the state in New Zealand in 1985 and showed that the country spent $2 million to treat 5,625 RF and RHD patients.[1] This represents an average cost of $355 per case per year. Hospital care, including heart surgery, represented 87 percent and ambulatory treatment 13 percent of the total expenditure. The average hospital stay was twenty-four days for RF, twenty-one days for RHD, and twenty-seven days for surgery (Neutze 1988b).

The indirect costs of RHD are quite high because it is primarily adolescents and young adults who are disabled or die during their most productive years. Mild carditis results in 10 percent disability and moderate carditis 25 percent disability for thirty years. Deaths from RHD are due to progressive heart failure and occur most often between the ages of twenty-five and thirty-four, on average twenty years after the initial RF attack. In addition, RHD causes approximately 50 percent disability during the twenty years preceding death. Thus, one can estimate the disability resulting from mild carditis to be three disability-adjusted life-years (DALYs) and the disability from moderate carditis to be six DALYs. Severe carditis causes the loss of twenty DALYs as a result of premature death and the loss of an additional ten DALYs, assuming that RHD causes 50 percent disability during the twenty years preceding death. The total indirect cost per RHD death, therefore, was estimated to be thirty DALYs.

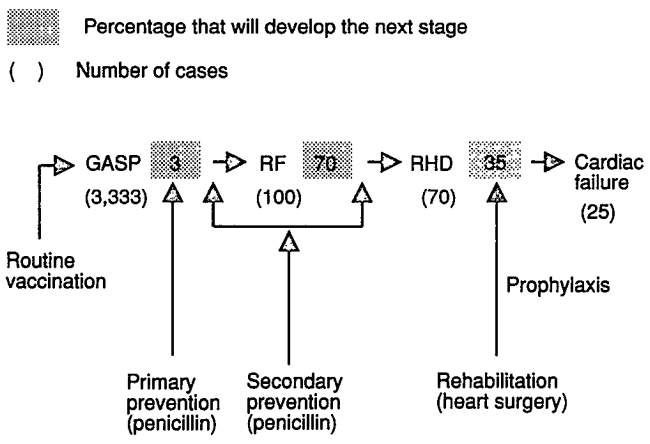
Elements of Preventive Strategy

Interventions to prevent RHD can be targeted at different points in the chain of events leading from GASP to intractable cardiac failure. Two different intervention strategies—mass penicillin prophylaxis or a vaccine—could prevent GASP. Mass chemoprophylaxis is not practical, however, unless the population at risk can be precisely targeted (for example, military recruits), and a vaccine is not yet available. Primary and secondary prevention therefore aim at reducing the occurrence of RF. Primary prevention averts the first attack of RF with a single injection of benzathine penicillin, and secondary prevention hinders recurrences of RF by providing monthly injections of benzathine penicillin. Finally, rehabilitation through cardiac surgery corrects damage to the valves and interrupts the progression to cardiac failure (figure 10-4).

Mass Chemoprophylaxis

Routine administration of benzathine penicillin injections was introduced among all U.S. military recruits after World War II because more than 20,000 cases of RF had occurred in navy and marine recruits between 1942 and 1945. The strategy was carried out effectively, and it prevented further epidemics of RF. Routine administration was discontinued in the early 1980s but was resumed after two outbreaks of RF occurred in 1986–87 at the naval training center in San Diego, California, and at the Fort Leonard Wood Army Training Base in Missouri. Both military epidemics were effectively terminated by the reintroduction of mass benzathine penicillin prophylaxis to all military recruits who were not allergic to penicillin (Bisno 1991).

Figure 10-4. Prevention of Rheumatic Fever and Rheumatic Heart Disease



Source: Authors, from epidemiological data.

Vaccine Development

A vaccine could prevent GASP, but vaccine development has been slow because initial vaccine candidates induced the production of antibodies that cross-reacted with the heart valves. A vaccine is unlikely to become available for several more years.

Recombinant DNA technology now provides the means to develop synthetic vaccines. An important first step toward the development of a synthetic vaccine was to discover the structure of M proteins and to learn the sequence of amino acids of different M proteins. M proteins encompass hypervariable and conserved regions. Hypervariable regions differ among different serotypes, but conserved regions are common to all serotypes. Protection against group A streptococci could be induced by antibodies directed to some conserved regions common to all M proteins (Fischetti 1991).

Primary Prevention

Primary prevention consists of a single injection of benzathine penicillin (or oral penicillin) each day for ten days to treat GASP effectively and prevent the occurrence of RF. Difficulties in finding cases and in establishing the diagnosis of GASP limit the effectiveness of this strategy. Primary prevention has been successful in industrial countries where GASP can be readily diagnosed. In many developing countries, however, GASP cannot be diagnosed because laboratory facilities required to identify group A streptococci are not available, and rapid antigen detection tests do not yet have the sensitivity required for a reliable diagnosis. Even where GASP can be diagnosed, the finding of cases is limited by biological factors, because GASP causes no symptoms in 30 to 50 percent of those who later develop RF. Children at greatest risk live in poor, overcrowded conditions and often have only limited access to health services.

In the absence of proper GASP diagnosis, the targeting required for effective primary prevention is impractical. Several hundred episodes of pharyngitis would have to be treated to prevent a single death from intractable cardiac failure (table 10-4). Twenty percent of all pharyngitis episodes are due to group A streptococci. Thus 333 out of 1,000 episodes of pharyngitis would be GASP and would lead to 10 cases of RF (3 percent), 7 cases of RHD (70 percent), and 2 or 3 deaths from intractable cardiac failure (35 percent). Because children remain at high risk between the ages of five and fifteen and commonly have pharyngitis at least twice a year, penicillin treatment would be required approximately twice a year for ten years to prevent RF effectively. Therefore, even though a single injection of benzathine penicillin costs only $3, averting one death would cost $40,920, or $1,049 per DALY (table 10-9).

Secondary Prevention

Long-term penicillin prophylaxis is the cornerstone of RF prevention in developing countries in which GASP cannot be diagnosed. It targets children who have had an initial attack of RF and consists of monthly injections of benzathine penicillin to prevent recurrences of GASP that might trigger new bouts of RF. Secondary prophylaxis should be given to those under the age of twenty-four for at least five years.

The advantage of secondary prophylaxis is that it targets a much smaller population, because only 3 percent of GASP episodes are followed by an initial attack of RF. Rheumatic fever cases are usually diagnosed when the patients seek treatment. In some instances, rheumatic carditis has been actively searched for among schoolchildren. Health care workers can be trained to note heart murmurs and to refer these children for further investigation.

The greatest challenge of secondary prevention is to ensure long-term compliance with monthly injections of benzathine penicillin for several years (Gordis, Lilienfeld, and Rodriguez 1969b; WHO Study Group 1988). In Hamilton, Australia, for instance, hospital contact was maintained by less than half of a group of RF patients during a ten-year period. Secondary prevention programs therefore require the establishment of a registry of RF/RHD patients and good coordination at various levels of the health system to ensure the proper follow-up of all RF patients.

Substantial experience now exists in many developing countries. The World Health Organization implemented secondary RF prevention programs in Barbados, Cyprus, Egypt, India, Iran, Mongolia, and Nigeria, as well as in several Latin American countries. In 1970 the cost of the program was estimated to be $325 per month, which was considerably less than the cost of maintaining pediatric beds at $1,260 per month (Hassell and Stuart 1974). The success of the programs nevertheless differed among countries. Compliance was considered adequate if fewer than 30 percent of benzathine penicillin injections were missed. In Barbados the introduction of RF identification cards and vigorous follow-up ensured compliance by 89 percent of all patients. In other countries, prophylaxis was effective in only 80 percent of the cases. The WHO study also demonstrated that patients who had only occasional or no penicillin prophylaxis at all spent on average six times as much hospitalization time as those on full prophylaxis (Strasser 1985). The importance of community participation was further demonstrated in Soweto, South Africa, where regular attendance to clinic-based prophylaxis increased from 17 percent to 38 percent seven months after a community outreach program was established (Edington and Gear 1982). In Thailand the National Control Program for RF/RHD was developed by an initial working group and was effectively implemented once it had been approved by the government. Ongoing evaluation provides the information required to make the necessary changes (Vongprateep, Dharmasakti, and Sindhavanonda 1988).

Cost estimates were based on the following assumptions: a benzathine penicillin prophylaxis once each month for five years and one hospitalization of twenty-four days for each initial RF attack to avert death among 34 percent of patients.

Under these assumptions, the cost of secondary prophylaxis to avert one death is $5,520, or $142 per DALY.

Tertiary Prophylaxis

Tertiary prophylaxis can reverse the progression of intractable cardiac insufficiency by means of surgical repair or replacement of damaged heart valves. Surgical interventions are important in developing countries because children and young adults often seek treatment when they already suffer from severe cardiac failure. The natural history of the disease demonstrates that surgical treatment is the only effective method in those instances (Antunes and others 1987).

Different types of surgical interventions exist to repair damaged heart valves: a mechanical valve prosthesis or biological valves are inserted in the heart to replace damaged heart valves; valvuloplasty conserves and repairs damaged valves rather than replacing them. Mechanical prostheses cause a high incidence of thromboembolic events which are potentially lethal, and anticoagulant therapy is required to avoid them; many biological valves degenerate early as a result of fibrosis and calcification, leading to early cardiac failure in young patients (Abid and others 1989). Thus despite immense strides in the perfection of materials and design, the ideal valve remains elusive. Consequently, the desirability of preservation of heart valves has become more appreciated. Valvuloplasty causes very few thromboembolic events. Monthly benzathine penicillin prophylaxis is required after surgery to prevent GASP and to avoid damage to the new cardiac valves (Antunes and others 1987).

The cost-effectiveness of those procedures needs careful evaluation because so many children and young adults suffer today from debilitating or intractable cardiac failure. Richard Bumgarner found that in China, out of 410,000 children suffering from RHD, 80,000 need valvular replacement (Bumgarner, personal communication). The mean cost of tertiary prophylaxis to avert one death is $12,750, or $425 per DALY (table 10-9). Tertiary prophylaxis is an attractive option despite high intervention costs.

Elements of Case Management Strategy

The experience gained thus far has led to the formulation of clear guidelines for the clinical management of cases of RF and RHD.

Acute Rheumatic Fever

The patient who has even a suspicion of RF should be hospitalized for diagnosis and initial treatment. In most secondary-level hospitals the diagnosis can be established according to Jones criteria. Other diagnostic procedures usually include chest x-ray, blood cell count, erythrocyte sedimentation rate, C-reactive protein, and ASO titer. A limitation in developing countries is the availability of a microbiological laboratory for throat culture and exclusion of infective endocarditis.

Once the diagnosis has been established, the management is straightforward:

- Eradication of group A streptococci from the throat by a course of penicillin.
- Acetylsalicylic acid (aspirin) or, in serious cases of carditis, corticosteroid treatment to suppress the accompanying inflammatory response. Response to acetylsalicylic acid and corticosteroid is so good that it should not be administered until the diagnosis is confirmed.
- Bed-chair rest in the hospital until cardiac manifestations subside, and mobilization when the acute phase reactants have returned to normal.
- In rare instances of severe carditis, cardiac valve replacement or valvuloplasty might be considered.
- Long-term penicillin prophylaxis.

Chronic Rheumatic Heart Disease

The initial management of the patient with RHD is directed at the control of heart failure. Cardiac arrhythmias are rare in young patients but increase with age. Cardiotonic (usually digitalis) is the appropriate drug to control arrhythmias and increase myocardial contractility. Diuretics are usually given to control fluid retention associated with heart failure. The most important therapeutic decision in RHD is the timing of surgical intervention, a costly tertiary prophylaxis requiring tertiary-care centers.

In all cases, with or without surgery, long-term penicillin prophylaxis and prophylaxis of bacterial endocarditis before other surgical procedures must be ensured.

Priorities

Secondary prophylaxis is the most cost-effective approach to prevent RF and RHD in developing countries. It is important to take into account the level of training of health care providers and the coverage of the health system while planning and implementing secondary prophylaxis in each country.

Priorities for Resource Allocation

Recent experiences in several developing countries have demonstrated that secondary prophylaxis is a cost-effective approach. In addition to providing penicillin, it is important to provide careful training of health care personnel in diagnosing heart murmurs and to ensure close follow-up of patients with RF and RHD by sensitizing health care providers and communities to the need for monthly penicillin injections. Where a good health care infrastructure is already in place, prevention of RHD can be included in national health plans with little added cost. In areas with little health coverage, populations at highest risk—school-age children of low socioeconomic groups enrolled in school in large urban areas—could receive special attention and secondary prophylaxis through the school system.

Priorities for Research

Further research is crucial to reduce the present burden of disease due to RF and RHD. New tools are needed to diagnose pharyngitis due to group A streptococci in developing countries and to produce a vaccine. Research is also important to monitor changes in the epidemiology of RF and RHD and to assess the effectiveness of interventions.

- Biomedical research is necessary to unravel fully the pathogenesis of RHD and to develop a simple diagnostic test and a vaccine.
- Epidemiologic research is important to assess the magnitude of the problem in different geographic areas and to monitor trends.
- Finally, operations research is essential to evaluate the effect of interventions.

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